UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/822,682	03/30/2001	Michael Streit	10287-051002 / MGH 1470.2	9232

26161 7590 03/05/2003

FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

EXAMINER
YU, MISOOK

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/05/2003

17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/822,682	STREIT ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *15* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

The Examiner of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Misook Yu.

DETAILED ACTION

Applicant's amendment, formal drawing, substitute specification, IDS, and Dr. Detmar's declaration filed on 11-25-2002 are acknowledged.

Claims 54-85 are pending and examined on merits.

Specification

The substitute specification filed on 11-25-2002 has not been entered because it does not conform to 37 CFR 1.125(b) because: it lacks a marked-up copy. Further it is not sure why a substitute specification was filed.

Information Disclosure Statement

The information disclosure statement filed 11-25-2002 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each **U.S.** and foreign **patent**; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. A copy of AA of the IDS is not provided. Further, AA is not US patent number. If applicant wants the Office consider a pending application in IDS, the pending application should be listed in 1449 with appropriate serial numbers.

Claim Rejections - 35 USC § 112

Enablement

Claims **54-80 remain rejected** and the **new claims 81-85 are also rejected** under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a cell expressing TSP-2, does not reasonably provide enablement for fragments and analogs. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to **use** the invention commensurate in scope with these claims. This rejection has several aspects.

Applicant argues that the rejection be withdrawn because the instant claims no longer recite "analog"; the instant claims are drawn to TSP at least 95 % identical to the sequences of SEQ ID NO:2 or a fragment thereof capable endothelical cell migration inhibition activity; it is a routine procedure in the art to make any size fragment or change any amino acid in a known protein such as TSP-2. Making various fragments or mutations in a known protein is a routine molecular biology technique but the Office maintains that undue experimentation is required to make a fragment that retains the function cited in the instant claims because the specification does not teach the specific structures responsible for inhibiting endothelical cell migration activity in light of the art recognized unpredictability in protein chemistry. Note the paragraph bridging page 3 and 4 of the previous Office action (Paper No. 11).

Claims 54-85 are not enabled for functional fragments of SEQ ID NO:2, an amino acid sequence at least 95 % identical to the sequences of SEQ ID NO:2, the various sequences in the new claims 81-85 other than SEQ ID NO:2 because the specification does not teach a method of treating a disorder using cell expressing the various other sequences or the fragments thereof other than SEQ ID NO:2. Applicant argues that the instant claims are enabled because as disclosed in Dr. Detmar's declaration along accompanying figures, the inventors found the specific N-terminal fragment nucleotides 213-1888 of SEQ ID NO:1 is effective. This argument is not convincing because the argument is directed to a limitation not in the claims.

Applicant further argues that TSP-2 cell therapy works as shown in Streit et al (Cancer Res 2002 April 1, vol. 62, pages 2004-12). This argument is not convincing because the instant specification (compare the instant specification at pages 62-69 to Streit et al, especially at page 2005 under Preparation of Polymer-cell Grafts and also the paragraph bridging left and right columns of page 2009) does not disclose all of the parameters necessary for inhibiting in vivo tumors and based on the disclosure in the instant specification, undue experimentation is necessary to practice the claimed invention.

Written Description

The new claims 81 and 82 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had **possession** of the claimed invention. Applicant argues that the instant claims are drawn to at least 95 % identical to SEQ ID NO:2 but this is not convincing because applicant argues with limitation not specified in the claims.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 57, and 81-85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 57 recites "aid" in line 2 but it is not clear what the metes and bounds are for the term.

Claim 81 recites "the nucleotide sequence of SEQ ID NO:2" but it is not clear what the metes and bound are for the limitation. The sequence listing of the instant specification indicates SEQ ID NO:2 is a protein sequence, not a nucleotide sequence.

Claims 54-85 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 54-85 are interpreted as drawn to method of cancer treatment using cell expressing TSP-2 or its functional fragments having endothelical cell migration activity. The active step of the instant invention is to administer cells expressing the proteins or its fragments. The instant specification

speculates at page 62-69 that cells expressing the protein or its fragments could be used to treat cancer. However, the specification fails to disclose in vivo demonstration of cancer treatment using the active steps of the instant invention. The in vivo data demonstrated in Fig. 3 of the instant application along with attached figures in Dr. Detmar's declaration filed on 11-25-2002 use gene therapy as active step, not the active steps claimed in the instant invention. Further, the specification does not disclose any in vivo disorder treatment using the active step of instant invention. The guidance and the example in the specification is administering a nucleic acid molecule and there is no example or guidance about administering cell expressing a protein. Streit et al (IDS, Cancer Res 2002 April 1, vol. 62, pages 2004-12) teach consideration necessary for successful cell-based therapy is different from the necessary consideration for successful gene therapy. Note Materials and Methods beginning at page 2004 of Streit et al. The specification does not teach how to all the steps necessary to make the transfected cells survive in vivo.

Further, cancer treatment or treatment of any other diseases listed in instant claim 80 is not a trivial matter. The specification does not teach any in vivo treatment method of any disease using the product in commensurate in scope of the invention. The art recognizes that method of treating cancer or any of the specific diseases listed in the instant claims is not trivial matter. It is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para of column 1). Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in

Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, one skilled in the art would accept without doubt the assertion that the claimed peptides or proteins would be useful for treating cancer. In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2).

Art recognizes cancer treatment is difficult and unpredictable. The specification provides insufficient guidance with regard to these issues and provides no working examples which would allow one of skill in the art to practice the invention without undue experimentation.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Misook Yu
March 3, 2003

SHEELA HUFF
PRIMARY EXAMINER